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A simple rhodium-catalyzed addition reaction of aldehydes with arylboronic acids in aqueous γ-valerolactone

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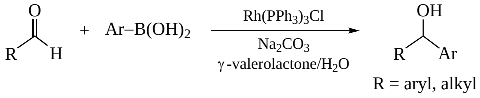
A simple rhodium-catalyzed addition reaction of aldehydes with arylboronic acids in aqueous γ-valerolactone provides the corresponding benzylic alcohols in moderate to good yields. Other organoboron reagents (boronic esters, aryltrifluoroborates, *etc*.) also showed good compatibilities, albeit with relatively lower yields.



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Diarylmethanols are useful building blocks in organic synthesis, for example, they serve as precursors for the synthesis of pharmaceutically active compounds.[1] The most straightforward way to access diarylmethanols involves the addition reaction of aryl aldehydes with organometallic reagents.[2–6] Among them, organoboron reagents have received much attention due to their excellent stability and commercial availability.[7] In 1998, Miyaura and co-workers reported the first rhodium-catalyzed addition reaction of arylboronic acids to aldehydes, providing the desired diarylmethanols in good yields.[8] Since then, many examples on Rh-catalyzed synthesis of diarylmethanols have been reported.[9–16] Asymmetrical[17,18] or heterogeneous synthetic routes were also successfully developed.[19,20] Recently, other metal catalysts including Pd,[21] Ni,[22] Ru,[23] Fe,[24] and Cu[25] complexes have been reported to catalyze this type of addition reaction.

Despite these tremendous achievements, most of the reactions required the use of expensive N or P ligands. Some procedures also suffer from the limitations such as harsh reaction conditions, limited substrate scope, or toxic solvents. Herein, we report on a rhodium-catalyzed addition reaction of aryl aldehydes with arylboronic acids in aqueous γ-valerolactone (GVL) without any ligands.

Initially, the reaction conditions were optimized using active 4-nitrobenzaldehyde **1a** and phenylboronic acid **2a** as the model substrates (Scheme 1, Table 1). Reaction in THF at 110 °C for 6 h afforded the desired product **3aa** in 87% yield with only 0.5 mol% of Rh(PPh$_3$)$_3$Cl. Reactions in other solvents such as Bu^{t}OMe, 1,4-dioxane, DMF, acetonitrile and water gave unsatisfactory yields (entries 1–3). Next, we tried this reaction using γ-valerolactone as the solvent due to its high boiling and flash points, low toxicity and good chemical stability.[26] Encouragingly, reaction in GVL afforded **3aa** in 89% yield, while reaction in ethyl acetate (EtOAc) or γ-butyrolactone (GBL) provided **3aa** in only moderate yields (entry 4). The combination of GVL and water turned out to be the best solvent, giving **3aa** in 99% yield (entry 5). It was assumed that addition of water would improve the solubility of the substrate and base in GVL. Other variations of conditions including reaction temperature, catalyst, reaction atmosphere and base were also evaluated (entries 6–11). The results indicated that the use of Rh(PPh$_3$)$_3$Cl as catalyst, Na$_2$CO$_3$ as base, GVL/water (1 : 1) as solvent under N$_2$ atmosphere at 110 °C was optimal.

With the optimized reaction conditions in hand, we tested a series of arylboronic acids **2a**–**r** (see Scheme 1).† Most of surveyed arylboronic acids showed good activities towards 4-nitrobenzaldehyde **1a** affording the corresponding products **3aa**–**ar** in moderate to good yields (45–99%). Generally,

Table 1 Optimization studies for the addition of 4-nitrobenzaldehyde **1a** with PhB(OH)$_2$ **2a**.[a]

Entry	Rh catalyst	base	Solvent	Yield of **3aa** (%)[b]
1	Rh(PPh$_3$)$_3$Cl	Na$_2$CO$_3$	THF	87 (12,[c] 74[d])
2	Rh(PPh$_3$)$_3$Cl	Na$_2$CO$_3$	DMF or MeCN	trace
3	Rh(PPh$_3$)$_3$Cl	Na$_2$CO$_3$	H$_2$O	58
4	Rh(PPh$_3$)$_3$Cl	Na$_2$CO$_3$	GVL	89 (60,[e] 61[f])
5	Rh(PPh$_3$)$_3$Cl	Na$_2$CO$_3$	GVL/H$_2$O (1 : 1)	99 (90,[g] 98,[h] 58[i])
6	[Rh(cod)Cl]$_2$	Na$_2$CO$_3$	GVL/H$_2$O (1 : 1)	85
7	RhCl$_3$	Na$_2$CO$_3$	GVL/H$_2$O (1 : 1)	13[j]
8	Rh(PPh$_3$)$_3$Cl	K$_2$CO$_3$	GVL/H$_2$O (1 : 1)	59
9	Rh(PPh$_3$)$_3$Cl	K$_3$PO$_4$	GVL/H$_2$O (1 : 1)	37
10	Rh(PPh$_3$)$_3$Cl	NaOH	GVL/H$_2$O (1 : 1)	trace
11	Rh(PPh$_3$)$_3$Cl	KF	GVL/H$_2$O (1 : 1)	64

[a] Reaction conditions: 4-nitrobenzaldehyde **1a** (0.2 mmol), phenylboronic acid **2a** (0.3 mmol, 1.5 equiv.), Rh catalyst (0.5 mol%), base (1.5 equiv.), solvent (2 ml), nitrogen, 110 °C, 6 h. [b] Isolated yield. [c] In Bu^{t}OMe. [d] In 1,4-dioxane. [e] In EtOAc. [f] In γ-butyrolactone. [g] At 100 °C. [h] At 120 °C. [i] Reaction under air. [j] Traces with Rh$_2$(OAc)$_4$.

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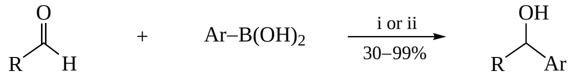
† *General procedure for the synthesis of* **3**. A sealed tube equipped with a magnetic stirrer bar was charged with **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), Rh(PPh$_3$)$_3$Cl (0.5 mol% or 1 mol%), Na$_2$CO$_3$ (0.3 mmol, 1.5 equiv.) and GVL/H$_2$O (1 : 1, 2 ml) under N$_2$. The reaction mixture was then heated to 110 °C and stirred for 6–12 h (for details, see Online Supplementary Materials). Upon reaction completion, the resulting solution was quenched with water and extracted with ethyl acetate. The collected organic extracts were dried over Na$_2$SO$_4$. The solvent was then removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (10 : 1) as eluent to afford the product (**3aa**–**ar** or **3ba**–**qa**).



1a–r **2a–r** **3aa–ar** **3ba–qa**

a R = 4-$O_2NC_6H_4$
b R = Ph
c R = 4-$MeOC_6H_4$
d R = 4-PhC_6H_4
e R = 4-FC_6H_4
f R = 4-$CF_3C_6H_4$
g R = 4-NCC_6H_4
h R = 2-$O_2NC_6H_4$
i R = 3-$O_2NC_6H_4$
j R = 4-HC(O)C_6H_4
k R = 4-$MeO_2CC_6H_4$
l R = 4-$Me_2NC_6H_4$
m R = 1-naphthyl
n R = 2-thienyl
o R = $PhCH_2$
p R = *n*-C_5H_{11}
q R = Bu^t

a Ar = Ph
b Ar = 2-MeC_6H_4
c Ar = 3-MeC_6H_4
d Ar = 4-MeC_6H_4
e Ar = 4-$Bu^tC_6H_4$
f Ar = 4-$H_2C{=}CHC_6H_4$
g Ar = 4-ClC_6H_4
h Ar = 4-BrC_6H_4
i Ar = 4-FC_6H_4
j Ar = 4-$CF_3C_6H_4$
k Ar = 4-$MeOC_6H_4$
l Ar = 4-$PhOC_6H_4$
m Ar = 4-$BnOC_6H_4$
n Ar = 4-NCC_6H_4
o Ar = 4-HC(O)C_6H_4
p Ar = 4-$EtO_2CC_6H_4$
q Ar = 4-PhC_6H_4
r Ar = 1-naphthyl

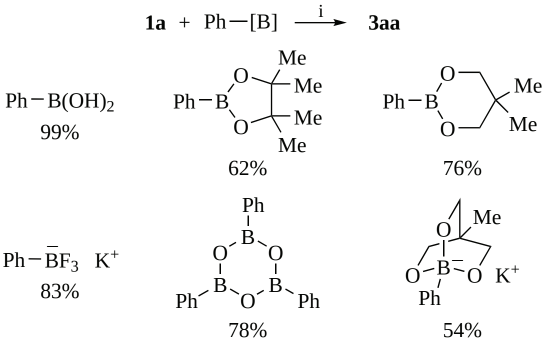
Scheme 1 *Reagents and conditions*: i (for products **3aa**–**ar**), **1a** (0.2 mmol), **2a**–**r** (0.3 mmol), $Rh(PPh_3)_3Cl$ (0.5 mol%), Na_2CO_3 (0.3 mmol), GVL/H_2O (1 : 1, 2 ml), N_2, 110 °C, 6 h; ii (for products **3ba**–**qa**), **1b**–**q** (0.2 mmol), **2a** (0.3 mmol), $Rh(PPh_3)_3Cl$ (1 mol%), Na_2CO_3 (0.3 mmol), GVL/H_2O (1 :1, 2 ml), N_2, 110 °C, 12 h.

electron-rich arylboronic acids were more active than electron-poor ones. Steric hindrance showed no influence on the reaction outcome (products **3ab**–**ad**). Arylboronic acids **2k**–**m**,**q**,**r** containing alkoxy, aryloxy, phenyl and naphthyl groups performed well under the standard reaction conditions. On the contrary, arylboronic acids **2n**,**o** with cyano and formyl groups were not compatible, and only moderate yields were achieved (55% for **3an** and 45% for **3ao**).

Different aldehydes were then screened using phenylboronic acid **2a** as the model substrate. Initial attempts revealed that results were not as satisfactory under the standard reaction conditions as for active 4-nitrobenzaldehyde **1a**. After further optimization (1 mol% catalyst, 12 h), most of the aromatic aldehydes reacted with **2a** smoothly to give the desired products **3ba**–**na** in good to excellent yields. Surprisingly, no reaction was observed when relative 4-methylbenzaldehyde was used. Steric hindrance showed no influence on the reaction since isomeric 2- and 3-nitrobenzaldehydes **1h**,**i** were converted into the corresponding alcohols **3ha** and **3ia** in yields of 95–96%. Formyl and dimethylamino and thiophene groups tolerated the reaction conditions, although the yields of products **3ja**, **3la** and **3na** were lower (40, 30 and 50%, respectively). Finally, some aliphatic aldehydes such as 2-phenylacetaldehyde **1o**, hexanal **1p** and pivalic aldehyde **1q** were evaluated, and good yields (72–85%) of alcohols **3oa**–**qa** were obtained.

Some organoboron reagents of other chemotypes were also tested (Scheme 2). Among them, phenylboronic acid exhibited the best result. Other organoboron reagents, although effective, provided the desired product **3aa** in relatively lower yields.

In summary, we have developed a simple rhodium-catalyzed addition reaction of aldehydes with arylboronic acids in aqueous γ-valerolactone. For this purpose, both aldehyde and arylboronic acid pools are broad enough. No other expensive ligand or cocatalyst is required in this reaction. The reactions proceeded smoothly to give a series of benzylic alcohols in moderate to good yields.



Scheme 2 *Reagents and conditions*: i, **1a** (0.2 mmol), ‘Ph–[B]’ (0.3 mmol), $Rh(PPh_3)_3Cl$ (0.5 mol%), Na_2CO_3 (0.3 mmol), GVL/H_2O (1 : 1, 2 ml), N_2, 110 °C, 6 h.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.036.

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